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A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose

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Three breast cancer risk factors were evaluated in terms of their interactions with radiation dose in a case-control interview study of Japanese A-bomb survivors. Cases and controls were matched on age at the time of the bombings and radiation dose, and dose-related risk was estimated from cohort rather than case-control data. Each factor—age at first full-term pregnancy, number of deliveries, and cumulative lactation period summed over births—conformed reasonably well to a multiplicative interaction model with radiation dose (the additive interactive model, in which the absolute excess risk associated with a factor is assumed to be independent of radiation dose, was rejected). An important implication of the finding is that early age at first full-term pregnancy, multiple births, and lengthy cumulative lactation are all protective against radiation-related, as well as baseline, breast cancer. Analyses by age at exposure to radiation suggest that, among women exposed to radiation in childhood or adolescence, a first full-term pregnancy at an early age *following* exposure may be protective against radiation-related risk. *Cancer Causes and Control 1994,* **5,** 167-176

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Introduction

This report is concerned with the joint effects on breast cancer risk of radiation dose and reproductive history, based on a case-control study of a fixed cohort of Japanese A-bomb survivors, the Life Span Study (LSS) sample of the Radiation Effects Research Foundation (RERF). As reported elsewhere in this issue,[1] that study identified several significant factors related to reproductive and medical history, as ascertained by interview and from an examination of medical and other records. Cohort-based studies of the LSS

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sample[2-6] have quantified a strong dose-response relationship between breast cancer risk and the ionizing radiation received from the atomic bombs dropped on Hiroshima and Nagasaki in August 1945. The present report is an examination of interactions between radiation dose and each of the major epidemiologic factors identified in the first report.

Excess breast cancer risk among women is one of the strongest and most thoroughly studied late health-effects of radiation exposure in this and other irradiated populations.[7] The following general observations apply to virtually all populations studied, and to the LSS cohort in particular. There is a marked dose response, with excess risk approximately proportional to the amount of radiation absorbed by breast tissue from several Gy down to less than 0.5 Gy. That dose response depends strongly upon age at exposure, with the highest dose-specific relative risks (RR) observed among women exposed as children or adolescents, and the lowest among women who were over 40 years of age when exposed. Regardless of age at exposure, no persuasive evidence of excess risk has been observed before about age 30, when baseline population rates begin to be appreciable. Among women exposed before age 20, radiation-related excess RR was several times higher before age 35 than later, a statistically significant difference that suggests the possible existence of a genetically susceptible population subgroup.[8] After age 35, regardless of age at exposure, the number of excess cases has increased with age at observation, in rough proportion (dependent on dose and age at the time of bombing [ATB]) to the increasing numbers expected in the absence of radiation exposure. One rather remarkable finding, based on analyses in parallel of incidence data from the LSS sample and from medically irradiated, patient populations in the United States, is that for similar radiation-dose levels, ages at exposure, and length of follow-up, similar excess rates (i.e., absolute risks) were observed despite three- to fivefold differences in age-specific population rates between the two countries.[9,10]

Radiation is but one of a number of factors whose relationships to breast cancer risk have been studied extensively and reported.[11-14] Population rates differ considerably by country, with Japan having among the lowest rates and America among the highest. Second and later-generation Americans of Japanese descent, however, especially those living in the continental US, have rates that approach those of Americans of European or African ancestry.[13,15] Within populations, nulliparous women have risks comparable to those of parous women whose first full-term pregnancies occurred at about age 30, while a first full-term pregnancy before age 18 is associated with a risk that is only one-third as high.[11] Studies differ on whether number of children and length of lactation history are independently related to risk or are merely strong negative correlates of age at first full-term pregnancy. Late age at menarche and early age at natural menopause are weakly protective (by 20 percent or more) in many studies, and a bilateral oophorectomy prior to menopause is strongly protective. First-degree relatives of women with breast cancer are at increased risk.

The question of interaction between radiation dose and other breast cancer risk factors is important for a number of reasons. One, which seems relatively minor because radiation doses from mammography examinations are low and because examinations generally are not given before age 35, is that women deemed for various reasons to be at unusually high risk of breast cancer might be especially sensitive to the carcinogenic effects of X-rays used in the examination. More generally, we hope through investigations of interaction to refine our estimates of radiation-related risk by taking proper account of ancillary information about populations and individuals at risk. Perhaps even more important from a long-term perspective is the possibility of gaining insights into why certain personal characteristics (e.g., number of children) are associated with increased or decreased breast cancer risk, by observing their modifying influences on the effects of an independent exposure to a known carcinogen *(i.e.,* ionizing radiation). We also may discover clues as to why radiation dose appears to be more effective in causing breast cancer when exposure occurs at young ages, and why radiation-related excess risk appears to track age-specific baseline risk so closely over time following exposure.

Materials and methods

The design and rationale of the case-control study are discussed at length in the companion paper *(i.e.,* Part I)[1] and in a separate methodologic report.[16] Here, the discussion is focused on aspects not necessary to the analysis of Part I, that is, those related to radiation dose and its interaction with the factors identified in Part I.

Study population

Breast cancer cases and controls were selected from the LSS sample,[17,18] a cohort defined on the basis of responses to an annex to the 1950 Japanese National Census. The cohort is a probability sample of A-bomb survivors, 55,000 of them female, resident in Hiroshima and Nagasaki on 1 October 1950, and a comparison group of nonexposed residents (15,000 females) identified on the basis of surveys taken between 1950

and 1953. The cohort has been under continuous surveillance for cause of death, a process that is virtually complete at the level of death certificate diagnosis,[18] and has been the basis for several studies of breast cancer incidence.[2-6] In an extraordinary early effort, cohort members were interviewed and, as the basis for individual radiation-dose estimates, their locations and shielding by buildings and terrain were ascertained.[19] At the time of case and control selection, 97.5 percent of the exposed cohort members had been assigned dose estimates according to the dosimetry system then in use, designated T65D.[19,20] In a continuing process beginning in 1986, the T65D dosimetry has been replaced by another, more refined system, designated DS86,[21,22] which is the present basis for dose-response analyses of the LSS cohort.

Study design

As discussed in Part I,[1] all LSS-sample breast cancer cases known to RERF through past incidence studies[4] and the local tumor and tissue registries[23] were selected for study, provided that they were living in the Hiroshima and Nagasaki areas. In all, 196 cases were available for interview. In addition, interviews were obtained from 566 control subjects not known to have breast cancer, who were selected from the same pool and individually matched to cases by city, age ATB, and estimated (T65D) radiation dose to breast tissue. A variable matching ratio was employed, with four controls originally chosen for each case with 0.5 Gy or more breast-tissue dose, or exposed in Nagasaki, and two controls per case otherwise. Cases and controls were interviewed in their homes, places of business, or in the RERF clinic, by RERF public health nurses trained as interviewers for this study. There was also limited follow-up interviewing by telephone when necessary to clarify certain items. The questionnaire employed was designed to elicit information on developmental and reproductive history prior to the diagnosis of cancer in the case and medical history, both general and gynecologic.

As discussed elsewhere,[16] the major design innovation for the study was to match cases with controls on the basis of estimated radiation dose to breast tissue as well as on city and age at exposure. The rationale was that all the information that could be obtained about radiation dose-response would be available from studies of breast cancer incidence in the entire LSS cohort, and that information about dose response from the case-control study therefore would be superfluous. Further, matching on radiation dose, and incidentally ensuring that the case-control study could provide no useful information about dose response, would minimize any need to adjust for radiation dose when investigating other variables as main effect factors. The most important consideration, however, was that matching on dose, and relying on cohort-based incidence data for information about radiation dose response, improves statistical power for investigating interactions with radiation dose.[16]

Statistical methods

All statistical comparisons were based on applications of the PECAN program for conditional likelihood analyses of matched case-control data,[24-25] If p_i is the probability, within matched set $s = s(i)$, that the i th subject is a case, and if $f(\beta, z_i)$ is the relative risk (more precisely, odds ratio [OR]) corresponding to covariate values represented by z_i where β denotes unknown parameters, then the basic underlying model can be written as

$$p_i/(1 - p_i) = \alpha_s f(\beta, z_i)$$

where α_s is the odds, among members of matched sets, of being a case and being sampled for the study when the relative risk function equals one. The parameters β of the relative risk (RR) function are estimated by conditioning on the covariate vectors observed in each set, using as the within-set likelihood the conditional probability of observing the covariate vector of the case.

In the analyses carried out for the Part I of this study, which was concerned with finding strong breast cancer risk factors other than radiation, a logistic model

$$f(\beta, z_i) = exp\ (\beta_1 z_{i,1} + ... + \beta_k z_{i,k}) \qquad (1)$$

was used for analyses of one or more risk factors $z_{i,j}$. The questions of interest in the present report involve

$$f(\beta, z, a, d) = (1 + \beta z)(1 + R(a,d)). \quad (3)$$

If the additive and multiplicative models are to be considered as alternatives, however, discriminating between them is more straightforward if they both can be subsumed into a more general parametric model, of which each is a special case. Many general models are possible, but for the present analysis considerations of computational convenience led to the model,

$$f(\beta, \theta, z, a, d) = [1 + R(a,d)][(1 + \beta z)/(1 + R(a,d))^{\theta}] \quad (4)$$

which reduces to the additive model (2) for $\theta = 1$ and to the multiplicative model (3) for $\theta = 0$. Thus, inferences about interaction are made in terms of the parameter θ. Here, $0 < \theta < 1$ corresponds to a model intermediate between (2) and (3), in which excess *absolute* risk per unit dose increases with increasing βz, but not as quickly as according to model (3) and excess *relative* risk per unit dose decreases, but not as quickly as according to model (2). If $\theta < 0$, then excess RR per unit dose increases with increasing βz ('super-multiplicative'), and if $1 < \theta$, excess absolute risk per unit dose decreases with increasing βz ('sub-additive').

Interaction analyses also were carried out in which the variable of interest, *z (e.g.*, age at first full-term pregnancy), was adjusted for another, *y (e.g.*, number of births). This was done by including the adjustment variable as an additional multiplicative factor in the model,

$$f(\alpha, \beta, \theta, y, z, a, d) = (1 + \alpha y)(1 + R(a,d))[1 + \beta z)/(1 + R(a,d))^{\theta}]. \quad (5)$$

In all analyses involving models like (2)-(5), the covariates represented by *y* and *z* were translated to have mean zero in the case-control set. This was done because the radiation dose-response coefficients *R(a,d)* used had been estimated from the entire cohort, without reference to the covariates of interest here. Thus they are defined with respect to a reference set with zero dose, zero age ATB, and covariates equal to their respective population means.[16] It follows, then, that the covariates should have the same reference set, which is accomplished, approximately, by translating each covariate by its sample mean in the case-control set.

Unless otherwise noted, all *P* values presented are two-tailed, and all confidence limits are two-sided limits at the 95 percent level.

Dosimetry and radiation dose-response

As mentioned previously, after all the interviews had taken place, the T65D dosimetry on which cases and controls had been matched was supplanted at RERF by a new dosimetry system, designated DS86. The new dosimetry was based on different assumptions about the radiation from the bombs and its attenuation by tissue and materials, and used different algorithms for estimating dose from the information previously obtained about cohort members.[21,22] Not surprisingly, cases and controls were not matched as closely in terms of the new dosimetry as for the old, but the problem was not serious: for study subjects with dose estimates according to both systems, the correlation was 92 percent. A more serious problem was that, because of a rigorous approach to dose estimation, many of the subjects (13 percent of the cases and 14 percent of the controls, compared with two percent of cases and three percent of controls for T65D) did not have DS86 dose estimates. This change did not affect Part I of the study, for which radiation dose was only a nuisance factor; also, as it turned out, there was little difference between the results of the interaction analyses performed using T65D and DS86 (analysis not shown).

For one case-control set included in Part I,[1] a case with dose two Gy had been matched erroneously to four controls whose doses were half as high. This set was dropped from the present analyses, for which matching on dose was more critical. Estimates of dose-specific excess RR were based on the following smooth functional relationship derived from the cohort-based incidence data for 1950-85:[6]

$$R(a,d) = d \exp(1.281 - 0.03735\, a) \quad (6)$$

where *a* is age ATB and *d* is equivalent radiation dose in Sv to breast tissue. The use of 'equivalent dose' indicates that *d* incorporates a correction (here, l0-fold) for the greater biologic effectiveness, compared with gamma rays, of the neutron component of the radiation from the bombs. In the remainder of this discussion, 'dose' should be understood to mean 'equivalent dose' in Sv.

In a separate analysis (manuscript in preparation), the statistical calculations reported here were shown to be affected only minimally by uncertainties consistent with confidence bands for *R(a,d)* or with likely random errors in individual dose values *d.*

Results

Summary of findings from Part I

In Part I of this study, three strong risk-factors were selected as representative of reproductive history: (i) age at first full-term pregnancy, with nulliparous women assigned an arbitrary age of 30; (ii) number of births; and (iii) cumulative lactation period, summed over all births. Factors (ii) and (iii) were correlated sufficiently in these data that neither was statistically significant after adjustment for the other; they are,

Table 1. Distribution of subjects (cases and controls) by age at time of bombing (ATB), age at diagnosis of the case, exposure status, and estimated radiation-related excess risk[a]

Age category (yrs)	Cases/ controls	Non-exposed[b]	Estimated excess relative risk due to radiation exposure (DS86)			Unknown DS86 dose
			$0 < R <= 0.05$	$0.05 < R <= 1$	$1 < R$	
Total	Cases	39	62	35	34	25
	Controls	88	152	96	148	76
0-9 ATB	Cases	1	2	2	5	0
	Controls	2	3	12	11	6
10-19 ATB	Cases	11	16	10	14	16
	Controls	25	44	26	68	41
20-29 ATB	Cases	8	18	14	8	7
	Controls	21	50	32	42	25
30-39 ATB	Cases	12	20	5	6	2
	Controls	26	41	19	19	4
40+ ATB	Cases	7	6	4	1	0
	Controls	14	14	9	8	0

[a] $R = R(a,d)$, where a is age ATB and d is estimated DS86 breast tissue dose.
[b] Not in either city ATB.

however, of independent interest in the epidemiologic literature and both are included in the present analysis.

Other reproductive history variables, such as age at menarche and age at menopause, were not clearly risk-related in these data even though such relationships have been observed fairly consistently in other populations.[11-15] One of the strongest predictors of risk in some other studies, a history of breast cancer among first-degree relatives, was subject to underascertainment, perhaps reflecting prevailing Japanese medical practices regarding patient access to information, and was not significantly related to risk. Two variables not usually associated with breast cancer— *i.e.*, gynecologic surgery and treatment for dysmenorrhea—were found to be associated positively with risk, the former with risk after age 55. These associations seemed questionable, however, because of the evidence cited above that respondents tended to be poorly informed about details of their own medical histories. Other variables significantly and positively associated with risk were, for risk after age 50, the Quetelet index (weight [kg]/ height $[cm]^2$; QI) at age 50 and, for risk after age 55, histories of thyroid disease and hypertension.

In Table 1, the numbers of cases and controls contributing to the present analysis are tabulated by age ATB and estimated radiation-related excess RR $R(a,d)$. It is noticeable that the loss of subjects due to missing DS86 dosimetry was greatest among the group of women exposed as teenagers. Of those subjects with and 60 (150) at age 55 or older; 69 (207) were premenopausal and 100 (277) were postmenopausal at the age of diagnosis (menopausal status was undetermined for one case, with two matched controls).

Interaction analysis

Table 2 shows the results of analyses according to the general model (4), of which the multiplicative and additive models are special cases corresponding to $\theta = 0$ and $\theta = 1$, respectively. On the basis of 95 percent confidence intervals (CI) for θ, which include zero but exclude one, and based on likelihood ratio test P values for the hypotheses $\theta = 0$ and $\theta = 1$, the data for the three main risk-factors were consistent with the multiplicative model and inconsistent with the additive model. For age at first full-term pregnancy in particular, the point estimate of θ was strongly negative, leaving little room for the possibility that the true interaction model is intermediate between multiplicative and additive. For all three variables, virtually the same results were obtained from analyses restricted to exposed subjects (analyses not shown); thus, the findings reflect interaction with dose, rather than with exposure *per se*. The corresponding analyses for the remaining five risk factors did not discriminate be-

Table 2. Summary of likelihood ratio (LR) test results for the additive and multiplicative models for interaction with radiation dose[a]

Risk factor	θ		LR tests *(P)*	
	Estimate	(CI)[b]	θ = 0	θ = 1
Age at 1st full-term pregnancy (yr)	–0.25	(–0.98-0.19)	0.16	0.0035
Number of births	–0.16	(–1.03-0.88)	0.34	0.044
Cumulative lactation (yr)	0.030	(–1.11-0.94)	0.93	0.046
Dysmenorrhea	0.44	(–1.20-45)[c]	0.65	0.72
Gyn. surgery (cancer dx. >= 55)	0.27	(–0.76-11.5)	0.71	0.54
Quetelet Index age 50 (cancer dx. > 50)	25.4	(–0.33-46)[c]	0.14	0.25
Thyroid disease (cancer dx. >= 55)	4.02	(–0.61-45)[c]	0.11	0.28
Hypertension (cancer dx. >= 55)	–0.24	[d]	0.77	0.37

[a] Model: $f(\beta, z,a,d) = [1 + R(a,d)][(1 + \beta z)/(1 + R(a,d))^{\theta}]$, where z is the risk factor of interest, a is age at exposure, d is DS86 radiation dose to breast tissue, and β and θ are unknown parameters.
[b] CI = 95% confidence interval.
[c] Maximum feasible value.
[d] Limit could not be computed.

mates, for nonexposed subjects, and for known-dose subjects with *R(a,d)* for the index case between zero and 0.05, between 0.05 and 1.0, and greater than 1.0, respectively. (Similar calculations for the remaining variables were uninformative, mainly due to small numbers.) As indicated by the analyses of Table 2, the estimated OR multipliers (exp (β)) in Table 3 are consistent with the multiplicative model, *i.e.*, they are approximately constant over exposure groups, and do not approach unity with increasing *R(a,d) as* they should according to the additive model.

Constancy of OR estimates with *R(a,d)* or a trend opposite in direction to that predicted by the additive model, imply that levels of the risk factor protective against baseline risk are also protective against radiation-related risk, and that levels which enhance baseline risk also enhance radiation-related risk following exposure. Thus, the results summarized in Table 2 indicate that a first full-term pregnancy at an early age, multiple births, and lengthy lactation history all are associated with reduced excess risk due to the radiation from the atomic bombings in this population.

Table 3. Conditional linear logistic model estimates of odds-ratio multipliers per unit risk factor increment, by estimated dose-related relative risk[a]

Risk factor	Dose/exposure category	OR[b]	(CI)[c]
Age at first full-term pregnancy (yrs)	Total	1.09	(1.04-1.13)
	Nonexposed	1.04	(0.93-1.16)
	0.00 < *R* <= 0.05	1.10	(1.02-1.18)
	0.05 < *R* <= 1.00	1.09	(1.00-1.18)
	1.00 < *R*	1.11	(1.02-1.22)
Number of births	Total	0.79	(0.71-0.88)
	Nonexposed	0.84	(0.66-1.03)
	0.00 < *R* <= 0.05	0.73	(0.60-0.87)
	0.05 <*R* <= 1.00	0.90	(0.68-1.18)
	1.00 < *R*	0.72	(0.52-0.95)
Cumulative lactation (yrs)	Total	0.78	(0.69-0.87)
	Nonexposed	0.84	(0.65-1.07)
	0.00< *R* <= 0.05	0.75	(0.61-0.91)
	0.05 < *R* <= 1.00	0.79	(0.57-1.05)
	1.00 < *R*	0.61	(0.42-0.84)

[a] Model: $f(\beta, z,a,d) = exp(\beta z)$, where z is the risk factor and β is an unknown parameter. The tabulated odds ratio estimate corresponds to $exp(\beta)$, and $R = R(a,d)$ is the dose-related excess relative risk for exposure to DS86 breast tissue dose d at age a.
[b] OR = odds ratio, multiplier per unit increment of the risk factor.
[c] CI = 95% confidence interval.

Interaction following adjustment for other variables

Further analyses (not shown) were conducted to evaluate the influence of correlated factors on the pattern of interaction of one risk factor with radiation dose. Using model (5), an interaction analysis was carried out for covariate *z* adjusted for covariate *y*. Number of births and cumulative lactation were not adjusted for each other, since they were not associated independently with risk.[1] After adjustment for age at first full-term pregnancy, neither the multiplicative nor the additive model could be rejected for number of births, which suggests that the non-additivity finding obtained in the analysis of Table 2 depended partly on the correlation between these two variables. In contrast, the interaction analyses for cumulative lactation gave results consistent with the multiplicative model but inconsistent with additivity, both before and after adjustment for age at first full-term pregnancy, and age at first full-term pregnancy remained significantly non-additive in the direction of multiplicativity after adjustment for either number of births or cumulative lactation.

Variation by age and menopausal status at diagnosis

Age-specific interaction analyses for the three main factors are presented in Table 4 by age and menopausal status at diagnosis. There was general consistency among results pertaining to diagnostic ages under 45, between 45 and 55, or 55 and older although, when the data were restricted to case-control sets with diagnosis ages 55 or older, discrimination between additivity and multiplicativity was poor for all three factors. Also, for diagnosis at ages younger than 45, discrimination was poor for number of births. Results of analyses restricted to premenopausal or postmenopausal risk were consistent with the age-specific results.

Variation by age ATB

There was little difference between results obtained for matched sets whose cases were under or over age 20 ATB (Table 5). Thus, in particular, an early age at first full-term pregnancy was apparently equally protective against radiation-induced breast cancer among women under 20 at exposure, few of whom had experienced a full-term pregnancy by that time, and among older women. When the analysis was restricted to sets with cases under 17 ATB, none of whose members had experienced a full-term pregnancy ATB, results were obtained similar to those for the under 20 ATB group ($\theta = -0.20$ with CI = –2.16-0.34); *P* values 0.25 for $\theta = 0$ and 0.011 for $\theta = 1$).

Discussion

This study provides clear evidence favoring a multiplicative, as opposed to additive, interaction model for

Table 4. Comparison of models for interaction with dose, for three major breast cancer risk factors, by age at breast cancer diagnosis [a]

Risk factor	Age or menopausal status at breast cancer diagnosis	θ		LR tests *(P)*	
		Estimate	(CI)[b]	θ = 0	θ = 1
Age at first full-term pregnancy	<45	0.00	(–1.34-1.07)	1.00	0.056
	45-54	–0.33	(–7.22-0.54)	0.24	0.027
	55+	–0.74	(c-45)	0.40	0.29
	Premenopausal	–0.07	(c-0.55)	0.67	0.017
	Postmenopausal	–0.82	(c-0.70)	0.13	0.042
Number of births	<45	–0.42	(–2.35-c)	0.40	0.21
	45-54	–0.30	(–1.10-1.72)	0.34	0.078
	55+	–0.18	(c-45)	0.59	0.29
	Premenopausal	0.00	c	1.00	0.24
	Postmenopausal	–1.33	(c-1.32)	0.29	0.061
Cumulative lactation (yrs)	<45	–0.43	(–1.08-c)	0.27	0.10
	45-54	–0.48	(–1.49-0.44)	0.13	0.025
	55+	–0.03	(c-45)	0.95	0.35
	Premenopausal	–0.32	(c-0.60)	0.19	0.028
	Postmenopausal	0.34	c	0.55	0.13

[a] Model: $f(\beta, z, a, d) = [1 + R(a,d)][(1 + \beta z)/(1 + R(a,d))^{\theta}]$, where *z* is the risk factor of interest, *a* is age at exposure, *d* is DS86 radiation dose to breast tissue, and β and θ are unknown parameters.
[b] CI = 95% confidence interval.
[c] Limit could not be computed.

Table 5. Comparison of models for interaction with dose, for three major breast cancer risk factors, by age ATB[a] of the index case in each matched set[b]

Risk factor	Age ATB	θ		LR tests (P)	
		Estimate	(CI)[c]	θ = 0	θ = 1
Age at first full-term pregnancy	<20	–0.54	(–3.48-0.10)	0.08	0.008
	20+	–0.18	(–0.97-2.22)	0.49	0.095
Number of births	<20	–0.84	[d]	0.25	0.097
	20+	–0.17	(–1.15-2.33)	0.42	0.091
Cumulative lactation (yrs)	<20	–0.45	([d]-1.71)	0.22	0.065
	20+	0.09	(–1.27-2.30)	0.78	0.12

[a] ATB = at time of bombing.
[b] Model: $f(\beta, z,a,d) = [1 + R(a,d)][(1 + \beta z)/(1 + R(a,d))^{\theta}]$, where z is the risk factor of interest, a is age at exposure, d is DS86 radiation dose to breast tissue, and β and θ are unknown or fixed parameters.
[c] CI = 95% confidence interval.
[d] Limit could not be computed.

radiation dose with each of three, strong, breast cancer risk factors defined in terms of reproductive history. Boice and Stone[26] analyzed data from a cohort of former tuberculosis patients exposed to multiple chest fluoroscopes, finding non-significant, 'super-additive' departures from additivity *(i.e.,* in the general direction of multiplicativity) for nulliparity and family history of breast cancer; their strongest epidemiologic risk factor, a history of benign breast disease, showed no evidence of departure from additivity. Shore *et al* [27] found no statistically significant departures from additivity between radiation dose and family history of breast cancer, late parity, or history of benign breast disease or hormone treatments among women treated by X-ray for acute postpartum mastitis. Marginally significant deviations were found for cystic breast disease occurring subsequent to irradiation (super-additive) and oral contraceptive use, also subsequent to irradiation (sub-additive). In another cohort study, Kato and Schull[28] found no evidence that higher socioeconomic status, which is associated generally with higher population levels of breast cancer risk, interacted non-additively with radiation dose among female A-bomb survivors.

In a study of the risk of second cancers arising in the contralateral breasts of women treated for breast cancer by radiotherapy, Boice *et al* [29] obtained estimates of excess risk per unit increment of tissue-dose to the contralateral breast, relative to that in women not treated by radiation, that agreed closely with predictions based on studies of North American patients given multiple chest fluoroscopes during treatment for tuberculosis. Thus, scatter radiation to the opposite breast has been shown to increase the already very high risk of a second cancer in women treated for a first breast cancer. Although the question of additive *cf* multiplicative interaction was not addressed specifically, the finding is consistent with a multiplicative interaction of radiation with unidentified factors responsible for elevated breast-cancer risk among former breast-cancer patients, compared with former tuberculosis patients or the general population.

The finding, mentioned earlier, that radiation-related risk, in absolute (as opposed to relative) terms, does not seem to be any greater among North American women exposed to medical X-ray than among Japanese women exposed to gamma rays and neutrons from the atomic bombs[9,10] implies that whatever causes American women to be at higher risk than Japanese women interacts approximately additively with radiation dose. On the other hand, excess RR appears to be fairly constant over time following radiation exposure; [5,6] apparently, whatever causes baseline breast-cancer risk to increase with age interacts multiplicatively with radiation dose. Thus, other data suggest that the two models seem to describe different aspects of breast cancer risk following radiation exposure. It is also of some interest that analyses of smoking and radiation exposure in relation to lung cancer risk among A-bomb survivors and uranium miners tend to suggest, although not conclusively, that the interaction between the two factors may be intermediate between the additive and multiplicative models.[30,31]

Our results suggest that, among women exposed to radiation from the atomic bombings, the risk of *radiation-induced* breast cancer has depended upon other factors besides the amount of radiation dose and the age at which exposure took place. A question requiring further investigation is the extent to which the obser-

vations reflect the influence of factors correlated with reproductive history or, alternatively, differential sensitivity to breast cancer initiation at various stages in a woman's reproductive life. Thus, women with early ages at first full-term pregnancy, as a group, might be at less risk following radiation exposure than other women of similar ages, because it is more likely that their first completed pregnancy occurred before exposure. Experimental work by Russo *et al* [32] suggests that differentiated breast cells are less susceptible to cancer initiation by the powerful carcinogens 7,12-dimethylbenz(a)anthracene and N-methylnitrosourea; the same may be true for ionizing radiation.

Alternatively, cell differentiation may reduce vulnerability to cancer promotion / progression even after initiation. In the present study, results of an analysis restricted to women under age 17 ATB suggest that experiencing a full-term pregnancy at a young age may protect against the carcinogenic effects of a previous radiation exposure. That finding is consistent with results obtained by Clifton *et al.* [33,34] In their experimental system, female rats were irradiated and then inoculated with prolactin-secreting, transplantable pituitary tumors. Half the rats were then adrenalectomized, precluding the secretion of adrenal corticoids necessary for cell differentiation for milk secretion. A high level of radiation-related mammary cancer was seen in the adrenalectomized animals, whereas among animals with intact adrenals, or receiving glucocortisol replacement therapy, the radiation dose-response was substantially less. The authors hypothesized that "in the presence of high levels of mammotropic hormone and adrenal corticoids, differentiation of a given cell for milk secretion reduced that cell's proliferative potential. When such differentiation was precluded by adrenocorticoid deficiency, more irradiation-altered cells retained their high proliferative potential and contributed to carcinoma formation. "

In the time since the cases and controls were selected for the present study, the number of breast cancer cases identified in the LSS sample has doubled; moreover, the great majority of the new cases have occurred among women under age 20 ATB.[6] Thus, further study of this population, using similar methods, may produce more refined estimates and resolve questions left unanswered here.

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